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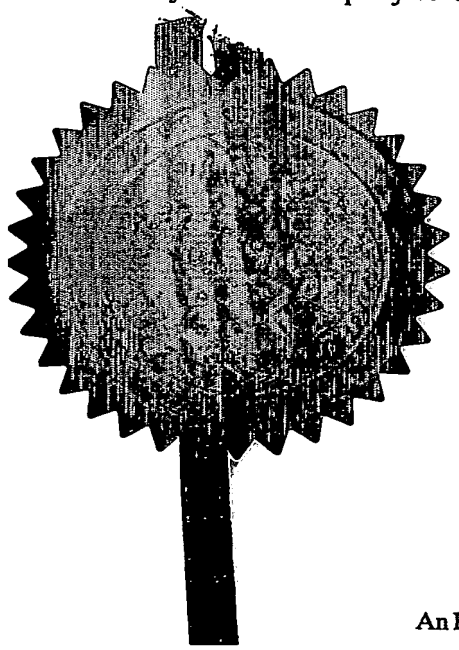

Signed

Dated 18 APR 2003

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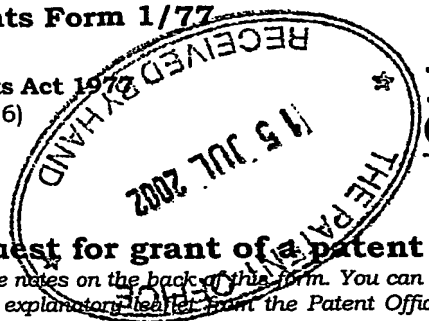

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The **Patent Office**

1/77

Request for grant of a patent

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The Patent Office
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1.	Your reference	G-32500P1/BCK 9919
2.	Patent application number *(The Patent Office will fill in this pa*	0216418.4
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	BIOCHEMIE GESELLSCHAFT MBH A-6250 KUNDL/TIROL AUSTRIA
	Patent ADP number *(if you know it)*	38991100 1
	If the applicant is a corporate body, give the country/state of its incorporation	AUSTRIA
4.	Title of invention	Organic compound.
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001 ✓

15 JUL 2002
16JUL02 E733520-1 D00524
P01/7700 0.00-0216418.4

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes		

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	7
Claim(s)	1
Abstract	1
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10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	ONE
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

B.A. Yorke & Co.

B.A. Yorke & Co. 15 July 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham
020 8560 5847

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Notes

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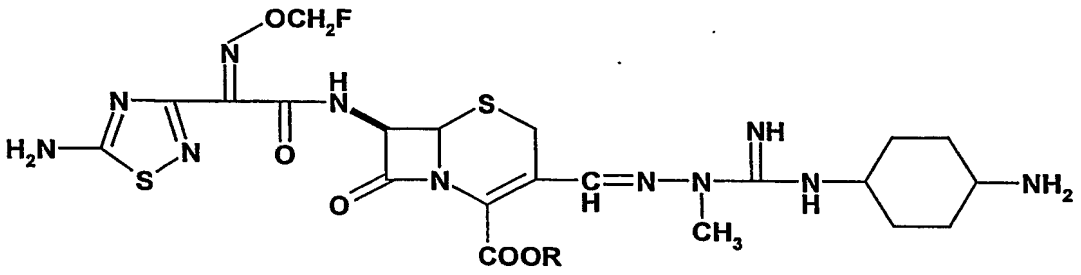
DUPLICATE

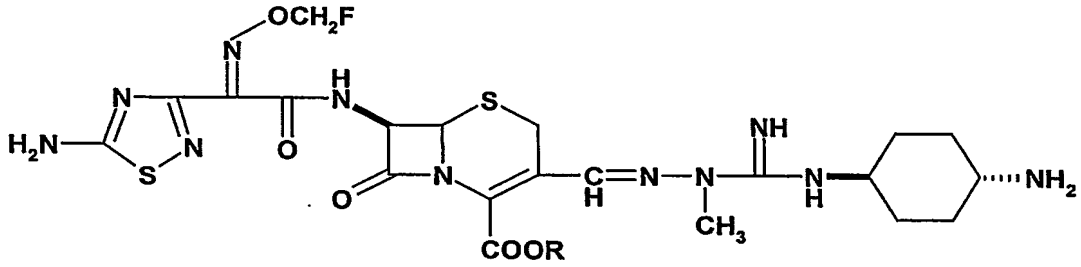
Organic Compound

The present invention relates to antibacterial compounds which are cephalosporines. Particularly the present invention provides a compound of formula



I

e.g. a compound of formula



I

wherein

R is H or an ester moiety.

If R is an ester moiety a compound of formula I may be in the form of an physiologically-hydrolysable and -acceptable ester. By physiologically-hydrolysable and -acceptable esters as used herein is meant an ester in which the COO- group is esterified and which is hydrolysable under physiological conditions to yield an acid which is itself physiologically tolerable at dosages to be administered. The term is thus to be understood as defining regular pro-drug forms. An ester moiety may be preferably a group which is easily hydrolysable under physiological conditions.

R in the meaning of an ester moiety includes e.g. alkyl, e.g. unsubstituted alkyl or substituted alkyl, e.g. by aryl, such as benzyl, alkoxybenzyl, such as 4-methoxybenzyl, alkoxy, such as methoxymethyl; alkyloxycarbonyloxy; alkyl; alkoxy, such as glycyloxy, phenylglycyloxy, e.g. glycyloxymethyl, phenylglycyloxymethyl; heterocyclyl e.g. 5-methyl-2-oxo-1,3-dioxolen-4-yl;

indanyl, phthalidyl, alkoxycarbonyloxy and ester moieties which form with the COO^- group a physiologically hydrolysable and acceptable ester, *e.g.* such known to be hydrolysable ester groups in the field of cephalosporins. Such esters may be administered preferably orally. Parenteral administration may be indicated if the ester *per se* is an active compound or, if hydrolysis occurs in the blood.

In this specification unless otherwise indicated the compound of formula I embraces the compound in any form, for example in the form of a salt and in free base form. The present invention thus includes a compound in free base form or, e.g. where such forms exist, in the form of a salt, for example in the form of an acid addition salt, inner salt, quaternary salt and/or in the form of a solvate, for example in the form of a hydrate. A salt may be a pharmaceutically acceptable salt of a compound of formula I such as a metal salt or an amine salt. Metal salts include for example sodium, potassium, calcium, barium, zinc, aluminum salts, preferably sodium or potassium salts. Amine salts include for example trialkylamine, procaine, dibenzylamine and benzylamine salts. A free form of a compound of formula I may be converted into a salt/solvate form and *vice versa*.

In a further aspect the present invention provides a compound of formula I in free form and in the form of a salt, for example an acid addition salt or a metal salt; and a compound of formula I, e.g. in free form or in the form of a salt, in the form of a solvate.

The present invention includes a compound of formula I in any isomeric from in which it may exist. E.g. the configuration may be syn [(Z)] and anti [(E)] and is preferably syn [(Z)]. E.g. geometric isomers may be obtained, e.g. during a production process of a compound of formula I, e.g. due to the presence of a -CH=CN- double bond. E.g. a chiral carbon atom may be introduced, e.g. during a production process of a compound of formula I and corresponding stereoisomeric forms of a compound of formula I may be obtained, e.g a mixture of the individual stereoisomers, e.g. a racemate, or pure isostereoisomeric forms. Mixtures of isomers may be separated.

The present invention includes a compound of formula I in any tautomeric form.

The compounds mentioned herein may be prepared as appropriate, e.g. according to a method as conventional or as disclosed herein.

In another aspect the present invention provides a process for the production of a compound of formula I by reaction of 4-amino-1((1-methylhydrazino)iminomethyl) with N-(1,4,5a,6-tetrahydro-3-hydroxy-1,7-dioxo-3H,7H-azeto(2,1-b)furo(3,4-d)(1,3)-thiazin-6-yl)-2-(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-2-(fluoromethoxyimino) acetic acid amide.

If desired, reactive groups in starting materials may be protected with protecting groups, which may be, or, which are split off under the reaction conditions, or after termination of the reaction. A compound of formula I wherein R is hydrogen may be converted into a compound of formula I wherein R is an carboxylic acid ester group and vice versa. A compound of formula I may be isolated from the reaction mixture as approptiate, e.g. according to a method as conventional.

The compounds of formula I including salt/solvate, hereinafter designated as "active compound(s) of the invention" exhibits pharmacological activity, e.g. beside low toxicity and are therefore useful as pharmaceuticals. In particular, the active compounds of the invention show antimicrobial, *e.g.* antibacterial, activity against e.g. gram negative and gram positive bacteria, e.g. gram positive bacteria such as Escherichia, e.g. Escherichia coli; Enterobacter, e.g. Enterobacter cloacae; Enterococcus, e.g. Enterococcus faecalis; Klebsiella, e.g. Klebsiella pneumoniae; Streptococcus, e.g. Streptococcus pneuminiae; Staphylococcus, e.g. Staphylococcus aureus; and Pseudomonas, e.g. Pseudomonas aeruginosa, in vitro in the Agar Dilution Test according to National Commitee for Clinical Laboratory Standards (NCCLS) 1993, Document M7-A3Vol.13, No. 25: "Methods for dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition, Approved Standard". The active compounds show an MIC (µg/ml) in the Agar Dilution Test from about <0.0125 to ca. >25.6. The active compounds of the invention show an surprising overall activity spectrum.

The active compounds of the present invention in the form of a salt exhibit the same order of activity as the active compounds of the present invention in free form; optionally in the form of a solvate.

In another aspect the present invention provides an active compound for use as a pharmaceutical, preferably as an antimicrobial agent, such as an antibiotic.

In a further aspect the present invention provides an active compound of the present invention for use in the preparation of a medicament for the treatment of microbial diseases, for example of diseases caused by bacterias selected from *Escherichia, Enterobacter, Enterococcus, Klebsiella, Streptococcus, Staphylococcus and Pseudomonas.*

In a further aspect the present invention provides a method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of an active compound of the present invention.

For this indication, the appropriate dosage will, of course, vary depending upon, for example, the compound of formula I employed, the host, the mode of administration and the nature and severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage is in the range from about 0.05 to 5 g, for example 0.1 to about 2.5 g, of an active compound of the invention conveniently administered, for example, in divided doses up to four times a day.

An active compound of the invention may be administered by any conventional route, for example orally, *e.g.* in form of tablets or capsules, or parenterally in the form of injectable solutions or suspensions, e.g. in analogous manner to ceftazidime.

Because of the compounds activity against various e.g. bacterial strains, compounds of formula I are indicated for the treatment of microbial diseases, *e.g.* bacterial diseases. The compounds of the invention may be administered to larger mammals, for example humans, by similar modes of administration at similar dosages than conventionally employed with ceftazidime.

The compound of formula I may be administered in pharmaceutically acceptable salt form, *e.g.* acid addition salt form or base addition salt form or in the corresponding free forms, optionally in solvate form. Such salts exhibit the same order of activity as the free forms.

The present invention also provides pharmaceutical compositions comprising an active compound of the present invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured accordingly, e.g. analogously to a method as conventional.

The present invention provides in further aspects

- an active compound of the present invention for use as a pharmaceutical in the treatment of microbial diseases caused by bacterias selected from Escherichia, Enterobacter, Enterococus, Klebsiella, Streptococcus, Staphylococcus and Pseudomonas;
- the use of an active compound of the present invention or the use of a pharmaceutical composition comprising an active compound of the present invention as a pharmaceutical and
- a method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of an active compound of the present invention.

Treatment includes disease treatment as well as prophylactic treatment.

Example 1:

a) Benzylidene derivative of trans-4-amino-1((1-methylhydrazino)iminomethyl)-cyclohexane monohydrochloride

35 g of the benzylidene derivative of S-methyl-2-methyl-isothiosemicarbazide hydrochloride and 32.79 g trans-1,4-diaminocyclohexane in 300 ml MeOH are refluxed and the reaction mixture is stirred at room temperature. A precipitate is formed, is filtered off, solvent from the filtrate obtained is removed and the residue obtained is treated with HCl. A precipitate is formed, is filtered off, washed and discharded. The volume of the filtrate obtained is brought to about 150 ml and the resulting suspension is kept over night at 4°C. A precipitate formed is filtered off, washed with water and acetonitrile, dried and recrystallized from water. 25.48 g of benzylidene derivative of trans-4-amino-1((1-methylhydrazino)iminomethyl)-cyclohexane in the form of a monohydrochloride are obtained as a solid.

b) trans-4-amino-1((1-methylhydrazino)iminomethyl)cyclohexane dihydrochloride

Benzaldehyde is distilled off by steam destillation from a mixture of 24.74 g benzylidene derivative of trans-4-amino-1((1-methylhydrazino)iminomethyl)cyclohexane in the form of a monohydrochloride and 79.9 ml 2 M HCl and solvent from the remaining mixture is evaporated off. 15.62 g of trans-4-amino-1((1-methylhydrazino)iminomethyl)-cyclohexane in the form of a dihydrochloride are obtained as a solid.

Example 2

a) 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-{2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-[(Z)-fluoromethoxyimino]-acetylamino}-cephem-4-carboxylic acid trihydrochloride

To a mixture of 2 g trans-4-amino-1((1-methylhydrazino)iminomethyl)cyclohexane in the form of a dihydrochloride in 3.4 ml 2 M HCl and 6.1 ml dimethylacetamide, 2.78 g of N-(1,4,5a,6-tetrahydro-3-hydroxy-1,7-dioxo-3H,7H-azeto(2,1-b)furo(3,4-d)(1,3)-thiazin-6-yl)-2-(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-2-(fluoromethoxyimino) acetic acid amide are added, the suspension obtained is stirred at room temperature and poured into 150 ml of acetonitrile under stirring. A precipitate formes, is filtrated off, washed and dried. 4.69 g of crude 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-{2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-[(Z)-fluoromethoxyimino]-acetylamino}-cephem-4-carboxylic acid trihydrochloride are obtained in the form of a powder.

b) 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-{2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-[(Z)-fluoromethoxyimino]-acetylamino}-cephem-4-carboxylic acid monohydrochloride

10 g of crude 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]-methyl}-7-{2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-[(Z)-fluoromethoxyimino]-acetylamino}-cephem-4-carboxylic acid in the form of a trihydrochloride are dissolved in 42 ml water and the dissolution obtained is subjected to chromatography (LiChroprep RP-18^R, Merck, grain size 40-63 um; eluens: 95/5 water/acetonitrile). Fractions containing the desired 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-{2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-[(Z)-fluoromethoxyimino]-acetylamino}-cephem-4-carboxylic acid monohydrochloride (HPLC determination) are combined and lyophilized.

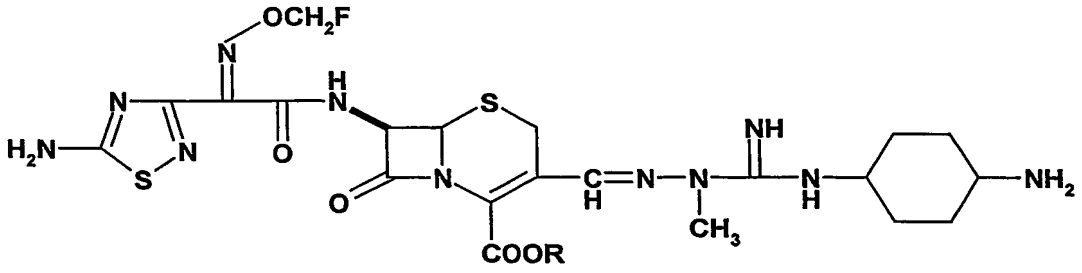
5.28 g of 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-{2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-[(Z)-fluoromethoxyimino]-acetylamino}-cephem-4-carboxylic acid in the form of a monohydrochloride are obtained as a lyophilizate.

^{1}H-NMR-Spectra (200 MHz, DMSO-d_6):

1.30 – 1.70, m, 4H, CCH_2; 1.80 – 2.10, m, 4H, CCH_2; 2.88 –3.10, m, 1H, NCH; 3.32, s, 3H, NCH_3; 3.42 – 3.70, m, 2H, 1H from SCH_2 and 1H from NCH; 4.25, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.28, d, J=5 Hz, 1H, ß-lactam; 5.79, d, J=55 Hz, 2H, CH_2F; 5,75, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.10, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

Claims:

1. A compound of formula



I

wherein

R is H or an ester moiety.

2. A compound according to claim 1 in the form of a salt or in the form of a solvate or in the form of a salt and a solvate.

3. A pharmaceutical composition comprising a compound according to any one of claims 1 to 2 in association with at least one pharmaceutical carrier or diluent.

4. Use of a compound according to any one of claims 1 to 2 as a pharmaceutical.

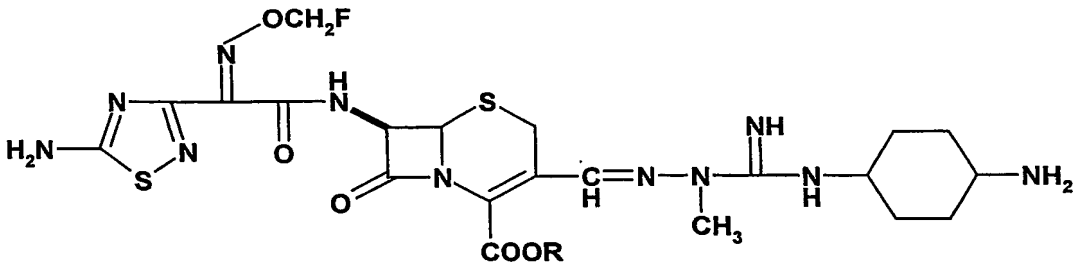
5. Use according to claim 4 in the treatment of microbial diseases.

6. A method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of a compound according to any one of claims 1 to 2 or a pharmaceutical composition according to claim 3.

IL/12-July-2002

Abstract:

A compound of formula



I

wherein

R is H or an ester moiety, useful as a pharmaceutical.

IL/12-July-2002